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SANOFI

DISEASE OBSERVATIONAL STUDY PROTOCOL WITH DISEASE PRIMARY DATA COLLECTION

Thromboembolic Risk and Mortality of Patients with Cold Agglutinin Disease (CAD) in European Countries: A Retrospective Chart Review

STUDY NUMBER: GER-CAD-19-11180

STUDY NAME: EU CAD chart review

The Study is conducted by Cerner Enviza

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1 SYNOPSIS

STUDY No:	**GER-CAD-19-11180**
TITLE	Thromboembolic Risk and Mortality of Patients with Cold Agglutinin Disease (CAD) in European Countries: A Retrospective Chart Review
LOCATION	EU countries: Germany, Italy, Austria
STUDY OBJECTIVES AND OUTCOMES	To better understand thrombotic events (TEs) and mortality in CAD
	Objectives / **Outcomes**
	Primary • To estimate incidence rates of thrombotic events (TEs) in CAD • Crude incidence rate of TE (overall and by type)
	Secondary • To characterize TEs in CAD and the risk factors for developing TE in CAD • Analysis of thromboembolic complications in patients with CAD: – Incidence rate of TE by type (arterial, venous) after CAD diagnosis – Cumulative incidence of TE after CAD diagnosis – Correlation between CAD-clinical severity and TE occurrence • To estimate mortality rates in CAD; all-cause, and by underlying cause • OS (Overall Survival) in CAD / mortality rate: – Mortality rate in CAD, all cause and cause-specific mortality – Overall survival • To assess health care resource utilization (HCRU) associated with TEs in CAD • Direct Health care resource utilization (HCRU) associated with TE in CAD: – Percentage of patients with TE-related inpatient hospitalizations, ER, ICU and outpatient visits – Length of stay of inpatient hospitalizations related to TEs – Number of procedures / surgeries associated with TE diagnosis and management
STUDY DESIGN & DURATION	This is a multinational, multicenter non-interventional study of all patients with a CAD diagnosis from January 1st, 2009 through January 1st, 2019 seen at hematology/oncology centers in European countries (Germany, Italy, Austria).

	Data from medical records from all eligible patients will be analyzed from the first relevant examination (January 2009 at the earliest) until the end of study follow-up on 1st January 2020, lost to follow-up or the patient's death. This time frame is based on consideration of a minimum time period required to achieve enrolment of the target number of patients, while excluding most recent follow-up period likely to have been impacted by the covid-19 pandemic. No visits, examinations, or procedures are mandated for this study. Demographic, clinical, and laboratory data will be extracted from medical records by using predesigned case report forms. Patient data will be de-identified, but a patient number will be assigned, and an identification key will be retained at each center. Informed consent will be obtained from enrolled patients allowing the use of their medical records for research (a waiver of informed consent may be obtained for deceased patients, lost to follow up patients and patients who did not visit the site during the documentation period, as per local regulations). Submissions to the respective Ethics Committees (EC)/Regulatory Authorities will be carried out in each country. In all countries, two different enrolled patient identification logs will be documented: one specific log for patients who signed an informed consent form, another specific one for dead patients, lost to follow up patients and for alive patients who did not visit the site during the data collection period. At the time of the database lock, and before the analysis, the specific enrolled patient identification log documented for dead patients, lost to follow up patients and for patients who did not visit the site during the data collection period, and where the unique identifier is documented, will be destroyed. Therefore, collected data will not be identifiable for these patients.
STUDY POPULATION	**Inclusion Criteria** • Age ≥18 years • An explicit cold AIHA (CAD) diagnosis in the patient medical chart between January 1st, 2009 and January 1st, 2019, based on: – Presence of chronic hemolysis AND – A positive direct antiglobulin test (DAT), with a typical DAT pattern of a positive monospecific test for C3d only OR – A positive direct antiglobulin test (DAT), with a typical DAT pattern of a weakly positive for IgG in addition to C3d • Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study. A request for a waiver of informed consent for patients deceased, lost to follow up or alive but did not visit the site at time of data collection will be requested, where applicable. As this study will be conducted in a real-world setting with treating physicians assessing CAD vs CAS, reported patients who were diagnosed with CAD but whose medical records do not capture the data required to define CAD using strict hemato-

	immunologic diagnosis criteria [ie High titer cold reactive antibody (CA) (most often defined as ≥64 at 4°C); CA with a thermal amplitude <30°C] will be included in the study and classified as "presumed CAD". **Exclusion Criteria** • Patient with any other form of hemolytic anemia, including CAS and mixed AIHA • Presence of records of any cause of secondary CAS at diagnosis [concurrent diagnosis of any type of lymphoma, multiple myeloma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, other active cancer, or recent infection with mycoplasma pneumoniae Epstein-Barr virus, cytomegalovirus, Autoimmune disorders (SLE)] **Expected number of patients**: Approx. 170
RECRUITMENT MODALITIES	**Selection of sites/investigators** A feasibility study will be run to select study sites/investigators able to reach recruitment goals and having the infrastructure or material resources necessary for completing the chart review study. A comprehensive list of hematology and oncology hospitals potentially managing CAD patients will be approached for the feasibility study in Germany. Referral centers of CAD expertise will be contacted in Italy and Austria. **Selection of patients** Study investigators routinely involved in the management of CAD patients (or delegates at the study site) will screen medical records of their patients diagnosed with CAD between January 1st, 2009 and January 1st, 2019 in a consecutive, retrospective order and include all those who fulfil pre-defined study eligibility criteria.
MAIN DATA COLLECTED	• Demographics: Date of birth (month, year); Sex • Relevant medical history: Any chronic or serious disease other than CAD and diagnostic date; Risk factors for TE; Previous medical history of TE • CAD characteristics: Age at onset of anemia or clinical symptoms; Age at diagnosis; Clinical presentation at or before diagnosis; Biological features at diagnosis; Transfusion history; Disease status over follow-up; History of hemolytic exacerbation/flares • Thromboembolic events: Type of TE events (arterial, venous) and other events such as post-thrombotic syndrome and pulmonary hypertension, and dates • Drug therapy associated with CAD: Agent/s (including any Corticosteroid Containing Therapy and Rituximab; Daily dose for corticosteroids; Duration of therapy, line of treatment; Treatment response (complete response, partial response, non-response); Splenectomy; Thromboprophylaxis

	• Direct HCRU associated with TE: All-cause inpatient admissions and length of stay (LOS); Outpatient visits; Admissions to ICU and LOS; Emergency room (ER) visits; Surgical and other major procedures • Patient vital status: Date of death; Cause of death
STATISTICAL METHODOLOGY	**Sample size calculation** The study aims to extract data from approximately 170 CAD patients from hospital chart reviews from hematology and oncology clinics offering specialized care for CAD patients in the countries of interest. Given the rarity of CAD, the number of patients included in the study is expected to be small. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable. The sample size is based on consideration of a minimum number of CAD patients required in terms of precision around expected TE incidence rates according to the literature. Assuming a TE incidence rate of 20-30% in CAD patients and a total sample of 170 CAD patients, the margin of error in the TE subgroup will be within ± 6.0 and 6.9% with an α risk of 95%. **Analysis** This study is primarily descriptive in nature and it does not include formal statistical hypothesis testing. All variables will be summarized descriptively through tabular displays of mean, median, ranges and standard deviations (SD) of continuous variables and frequency distributions of categorical variables. Changes in disease activity closest to the date of each study event will be described, where data are available. Crude incidence rates (with 95% CI) will be calculated from the number of TE after CAD diagnosis and the sum of individual person-years contributed by the CAD population during the study period. The mortality rate will also be estimated in this way. For event analysis, the main events evaluated will include time to first TE and time to death. The cumulative incidence of TE will be estimated using Kaplan-Meier survival analysis accounting for mortality as a competing risk event if sample size allows it. Descriptive analysis will be used to identify risk factors associated with occurrence of TE. Per-patient-per-month (PPPM) HCRU, will be calculated during the variable follow-up period of up to 12 months after the TE diagnosis. Both “confirmed” and “presumed” CAD patients will be included in the primary analysis. Sensitivity analyses will be performed to address any potential misclassification in CAD diagnosis. An interim analysis will be performed when the documentation of two out of three countries is completed, and when minimum number of patients have been included in two countries. A global report ~~and a specific report for Italy~~ will be written.

primary data collection

Study Number: GER-CAD-19-11180 Version number: ~~V6~~V7.0

ESTIMATED DURATION OF THE STUDY	Estimated enrollment duration: ~~10~~ 14 months Estimated dates: end-August 2022 – ~~end~~arly ~~June~~October 2023 First Site Active: August 29th, 2022 Last Site Active: ~~end of April~~October 2023 Last Data In: ~~end of June~~October 2023

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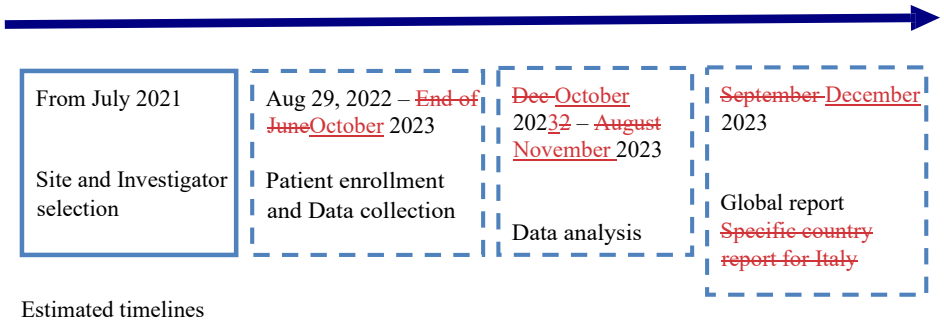
2 FLOW CHARTS

2.1 GRAPHICAL STUDY DESIGN



Estimated timelines

2.2 STUDY FLOW CHART

The study consists of the documentation of an e-CRF for adult patients with CAD (please refer to Section 10.1 for details).

Note: The observational study operates under real clinical practice conditions; it collects only available data and necessary data for the purpose. There are no imposed protocol visits or procedures.

Study Flow Chart

Evaluation	Inclusion	Retrospective Eligibility Period: At CAD diagnosis between January 1st, 2009 – January 1st, 2019 (index date)	Retrospective Patient Follow-up: From the index date until study end (January 1st, 2020) or patient death or lost to follow-up, whichever occurs first
Informed consent form	Date of next routine consultation at the site (Italy only, for patients to sign the ICF at site as per local regulation)	Signature of the ICF prior to data collection	
Inclusion criteria	• Adult patients aged ≥18 years • Patients who fully meet the diagnostic criteria (see opposite) • Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study	After they agree signing the informed consent form, adult patients aged ≥18 years diagnosed between January 1st, 2009 and January 1st, 2019 with an explicit cold AIHA (CAD) based on: • Presence of chronic hemolysis AND • A positive direct antiglobulin test (DAT), with a typical DAT pattern of a positive monospecific test for C3d only OR • A positive direct antiglobulin test (DAT), with a typical DAT pattern of a weakly positive for IgG in addition to C3d	
Exclusion criteria	N/A	• Patient with any other form of hemolytic anemia, including CAS and mixed AIHA • Presence of records of any cause of secondary CAS, [e.g. a concurrent diagnosis of any type of lymphoma, multiple myelomas, chronic lymphocytic leukemia, Waldenström macroglobulinemia, other active cancer, or recent infection with mycoplasma pneumoniae, Epstein-Barr virus, cytomegalovirus; autoimmune diseases (SLE)]	
Patient demographics	Date of birth (month, year); Sex	N/A	N/A
Relevant medical history	N/A	• Any chronic or serious disease other than CAD and diagnostic date • Risk factors for TE • Medical history of TE	N/A
CAD characteristics	N/A	• Age at onset of anemia or clinical symptoms • Age at diagnosis • Clinical presentation at or before diagnosis • Biological features at diagnosis • Transfusion history	• Disease status over follow-up • History of hemolytic exacerbation/flares
Thromboembolic events	N/A	• Type of TE events (arterial and venous) and other events and dates • Situational circumstances in the weeks prior to a TE	

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primary data collection

Drug therapy associated with CAD	N/A	• Agent/s (including any Corticosteroid Containing Therapy and Rituximab) • Daily dose for corticosteroids • Duration of therapy, line of treatment • Treatment response (complete response, partial response, non-response) • Splenectomy • Thromboprophylaxis	
Direct HCRU associated with TE	N/A	N/A	• All-cause inpatient admissions and length of stay (LOS) • Outpatient visits • Admissions to ICU and LOS • Emergency room (ER) visits • Surgical and other major procedures
Patient vital status	N/A	N/A	Date of death Cause of death

AIHA: autoimmune hemolytic anemia; CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; DAT: Direct Antiglobulin Test; DVT: Deep Venous Thrombosis; ER: Emergency room; ICF: Informed Consent Form; ICU: Intensive Care Unit; IgG: Immunoglobulin G; LOS: length of stay; N/A: Not Applicable; PE: Pulmonary Embolism

3 TABLE OF CONTENTS

Signature Page 1

1 SYNOPSIS 5

2 FLOW CHARTS 10

2.1 GRAPHICAL STUDY DESIGN 10

2.2 STUDY FLOW CHART 10

3 TABLE OF CONTENTS 13

4 LIST OF ABBREVIATIONS 15

5 INTRODUCTION AND RATIONALE 16

5.1 INTRODUCTION 16

5.2 RATIONALE 18

6 STUDY OBJECTIVES AND OUTCOMES 19

7 STUDY DESIGN 20

7.1 DESCRIPTION OF THE STUDY DESIGN 20

7.2 DURATION OF STUDY PARTICIPATION FOR EACH PARTICIPANT 21

8 SELECTION OF PARTICIPANTS 22

8.1 NUMBER OF PARTICIPANTS 22

8.2 INCLUSION CRITERIA 22

8.3 EXCLUSION CRITERIA 22

8.4 MODALITIES OF RECRUITMENT 23

9 SELECTION OF INVESTIGATORS 24

10 DATA COLLECTION 25

10.1 DATA COLLECTION SCHEDULE 25

10.2 DEFINITION OF SOURCE DATA 26

10.3 DATA COLLECTED 26

10.3.1 Participant data 26

10.3.2 Site/Investigator questionnaire 28

10.3.3 Participant tracking log (if applicable) 28

10.4 PROCEDURE AND CONSEQUENCE FOR PARTICIPANT WITHDRAWAL FROM STUDY 28

11 MANAGEMENT OF DATA 30

11.1 DATA COLLECTION, VALIDATION AND DATA QUALITY CONTROL AT CERNER ENVIZA LEVEL 30

11.2 MONITORING AND DATA QUALITY CONTROL AT SITE LEVEL 31

12 PHARMACOVIGILANCE 32

13 STATISTICAL CONSIDERATIONS 33

13.1 DETERMINATION OF SAMPLE SIZE 33

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13.2 DISPOSITION OF PARTICIPANTS 34
13.3 ANALYSIS POPULATIONS 34
13.4 STATISTICAL METHODS 34
13.5 EARLY ANALYSIS 35
14 RESPONSIBILITIES 36
14.1 RESPONSIBILITIES OF STUDY COMMITTEES 36
14.2 RESPONSIBILITIES OF THE INVESTIGATORS 37
14.3 RESPONSIBILITIES OF CERNER ENVIZA 37
15 ETHICAL AND REGULATORY STANDARDS 38
15.1 ETHICAL PRINCIPLES 38
16 ADMINISTRATIVE EXPECTATIONS 39
16.1 RECORD RETENTION IN STUDY SITE 39
16.2 CONFIDENTIALITY 39
16.3 DATA PROTECTION 40
16.4 DISSEMINATION OF STUDY DATA 44
16.5 INSURANCE 45
16.6 SANOFI-AVENTIS GROUPE OR CERNER ENVIZA AUDITS AND INSPECTIONS BY REGULATORY AGENCIES 45
16.7 PREMATURE DISCONTINUATION OF THE STUDY 46
16.8 OWNERSHIP AND USE OF DATA AND STUDY RESULTS 46
16.9 PUBLICATIONS 46
17 PROTOCOL AMENDMENTS 47
18 BIBLIOGRAPHIC REFERENCES 49

4 LIST OF ABBREVIATIONS

AIHA	AutoImmune Hemolytic Anemia
CAD	Cold Agglutinin Disease
CAS	Cold Agglutinin Syndrome
CVC	Cardio-Vascular Condition
DAT	Direct Antiglobulin Test
DVT	Deep Venous Thrombosis
EC	Ethics Committee
ER	Emergency room
HCRU	Health Care Resource Utilization
ICF	Informed Consent Form
ICU	Intensive Care Unit
IgG	Immunoglobulin G
LDH	Lactate DeHydrogenase
LOS	Length Of Stay
N/A	Not Applicable
PE	Pulmonary Embolism
PPPM	Per Patient Per Month
SLE	Systemic Lupus Erythematosus
TE	Thromboembolic event
VTE	Venous ThromboEmbolism.

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5 INTRODUCTION AND RATIONALE

5.1 INTRODUCTION

Cold agglutinin-mediated autoimmune haemolytic anaemia (cold agglutinin-mediated AIHA) is a complement-mediated haemolytic disorder in which clonal or oligoclonal IgM antibody binds to red blood cell (RBC) antigens in sites of the body where the temperature is low (i.e. cold agglutinins). This leads to RBC agglutination and activation of the classical complement pathway and extravascular hemolysis (1, 2). Cold agglutinin-mediated AIHA can occur in the setting of an underlying viral infection, lymphoid malignancy or autoimmune disorders such as systemic sclerosis (scleroderma) and rheumatoid arthritis (3, 4), and is then referred to as secondary cold-agglutinin syndrome (CAS). Most cases arise without one of these underlying disorders and are thought to originate from a low-grade lymphoproliferative disorder. They are referred to as cold agglutinin disease (CAD)

The prevalence of CAD is estimated to be 16.2 cases per million, with an incidence rate of 1.0 case per million person-years; these estimates may be several fold higher in colder climates (5). Studies have demonstrated a slightly higher prevalence in females and a mean age at presentation in the mid to late 60s, with a broad range (30s to 90s) (5-7).

Most common clinical manifestations include cold-induced symptoms (mostly acrocyanosis), usually present in 52 % of patients, or up to 90% in colder climates such as in Scandinavia (5, 7). Ninety per cent of cases present anaemia (median haemoglobin, 9.5 g/dL, with some individuals in the normal range and others as low as 4.5 g/dL) (5-7). Symptoms attributable to anaemia include fatigue, shortness of breath, asthenia, angina and dyspnoea, which can be associated with substantial impairment in quality of life. Ninety per cent of cases present markers of haemolysis (high lactate dehydrogenase [LDH] and bilirubin, low haptoglobin). The severity of haemolysis can range from compensated haemolysis without anaemia to severe haemolytic anaemia requiring transfusion (5, 7). Spontaneous exacerbations and remissions in the course of the disease are to be expected, e.g. some individuals may have chronic compensated haemolytic anaemia with episodes of more severe anaemia due to increased haemolysis precipitated by cold temperatures or by febrile or other acute illnesses (e.g. episodes of the common cold, pneumonia). Therefore, patient needs for RBC transfusions fluctuate over time according to the occurrence of severe anaemia and individuals with mild disease may only require transfusions in the setting of severe haemolysis precipitated by infection or during the winter months (5, 8). Overall, the extent of

CAD subjects utilizing RBC transfusions, either preceding diagnosis or during follow-up ranges from 40% to 100% (5).

While twenty four percent of patients are treated with supportive/symptomatic care alone (5), the remaining 76 % receive off-label CAD-directed medical therapy to reduce antibody production and maintain an acceptable haemoglobin levels (9, 10). Therapy generally involves rituximab in combination or as monotherapy, or bortezomib for individuals for whom a rituximab-containing regimen is ineffective or contraindicated (9). Randomized trials to assess the efficacy of rituximab in CAD have not been performed, but case series have reported response rates of more than 50 percent; many of the responses are partial (complete responses observed in only 21% of CAD patients) and with a slow response time (11, 12). Many patients continue to relapse despite the use of multiple lines of therapy, the median duration of response ranging from 6.5 to 11 months (11, 13).

Overall, the prognosis of CAD patients depends on the severity of the disease, with a median overall survival of 10.6 to 12.5 years from disease onset (5-7). Mortality in CAD patients has been reported to be significantly increased compared with a general population matched cohort (19). Causes of death include severe anaemia complications, ischemic stroke, and infection. However, information on mortality is limited, with most of the CAD-related literature being composed of case reports and small case series, and several methodological issues should be considered when interpreting existing data for larger cohorts.

CAD and risk of thromboembolic events (TEs)

Recent data suggest a correlation between CAD and thromboembolic events (TEs), which can impact quality of life and also lead to premature mortality (14, 15). TEs can also substantially increase disease burden and cost of treatment in CAD; in the general population, ten to thirty percent of patients die within 1 month of diagnosis of a venous thrombotic event (VTE), and among those who survive, 50% have long-term complications (16). An incident VTE has been estimated to cost between $12 000 and $15 000 in 2014 in the USA, which increased to $18 000-$23 000 when including subsequent complications (17).

Nevertheless, TE data in CAD is sparse, and the rarity of CAD limits the ability to perform large population-based studies. Several methodological limitations should be considered when interpreting existing TE data from the largest population-based studies in CAD and TE; a retrospective study in the USA involving a cohort of 608 individuals diagnosed with CAD from an insurance-based registry and nearly 6,000 matched controls recorded (venous and arterial) TE

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during a 10-year period in 30 percent of those with CAD versus 18 percent of controls (adjusted hazard ratio [HR], 1.94; 95% confidence interval [CI], 1.64-2.30) (18), but misclassification due to coding errors inherent to claims data is likely. A smaller study from a Danish registry found an increased rate of TE in CAD patients as compared with age- and sex-matched controls (19), but there were also some methodology issues associated with the lack of validation of diagnostic codes in such registry.

5.2 RATIONALE

Therapies that target the classical complement pathway components responsible for extravascular hemolysis in CAD are under investigation. Sutimlimab is a humanized monoclonal antibody that targets C1s and has the potential to reduce extravascular hemolysis mediated by C3b (1, 20-23). Its efficacy was demonstrated in a small series of 10 patients with primary CAD and ongoing hemolytic anemia (24). An extension study in which sutimlimab was given as maintenance therapy demonstrated sustained improvements in hemoglobin and suppression of hemolysis (25).

In the context of the coming introduction of sutimlimab and other new therapies in Germany, Italy and Austria, it is important to collect up-to-date and comprehensive data on the burden of CAD on patients and the health care system in these countries. Due to the limited data from longitudinal studies on the incidence of TE, TE-related mortality, risk factors and impact on healthcare resource utilisation (HCRU) in CAD patients, this study will analyse TE incidence and mortality as documented in CAD patient medical records in the countries of interest. Results will be used to inform the future local HTA dossier submissions for sutimlimab across the European region. This information will also be important to achieve greater awareness among health care providers about the burden of this disease and inform about CAD patients who might be at risk of TEs and mortality. This data, which will be made publicly available, may ultimately help to promote implementation of appropriate prevention strategies, diagnosis of TE, and patient management.

6 STUDY OBJECTIVES AND OUTCOMES

The study objectives are to better understand thrombotic events (TEs) and mortality in CAD:

Primary objective

- To estimate incidence rates of thrombotic events (TE) in CAD

Secondary objective(s)

- To characterize TEs in CAD and the risk factors for developing TE in CAD
- To estimate mortality rates in CAD, all-cause, and by underlying cause
- To characterize health care resource utilization (HCRU) associated with TEs in CAD.

Table 1 - Objectives and outcomes

	Objectives	Outcomes
Primary	• To estimate incidence rates of thrombotic events (TEs) in CAD	• Crude incidence rate of TE (overall and by type)
Secondary	• To characterize TEs in CAD and the risk factors for developing TE in CAD • To estimate mortality rates in CAD, all-cause, and by underlying cause • To assess health care resource utilization (HCRU) associated with TEs in CAD	• Analysis of thromboembolic complications in patients with CAD: – Incidence rate of TE by type (arterial, venous) after CAD diagnosis – Cumulative incidence of TE after CAD diagnosis – Correlation between CAD-clinical severity and TE occurrence • OS (Overall Survival) in CAD / mortality rate: – Mortality rate in CAD, all cause and cause-specific mortality – Overall survival • Direct HCRU associated with TE in CAD: – Percentage of patients with TE-related inpatient hospitalizations, ER, ICU and outpatient visits – Length of stay of inpatient hospitalizations related to TEs – Number of procedures / surgeries associated with TE diagnosis and management

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7 STUDY DESIGN

Operational criteria for CAD definition are as follows:
An explicit cold AIHA (CAD) diagnosis in the patient medical chart between January 1st, 2009 and January 1st, 2019, based on:

- Presence of chronic hemolysis
- A positive direct antiglobulin test (DAT), with a typical DAT pattern of a positive monospecific test for C3d only
  OR
  A positive direct antiglobulin test (DAT), with a typical DAT pattern of a weakly positive for IgG in addition to C3d
- Absence of records of any cause of secondary CAS, [e.g. a concurrent diagnosis of any type of lymphoma, multiple myeloma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, other active cancer, or recent infection with mycoplasma pneumoniae, Epstein-Barr virus, cytomegalovirus, autoimmune disorders (SLE)]

However, as this study will be conducted in a real-world setting with treating physicians assessing CAD vs CAS, reported patients who were diagnosed with CAD but whose medical records do not capture the data required to define CAD using strict haemato-immunologic diagnosis criteria (High titer cold reactive antibody (CA) (most often defined as ≥ 64 at 4°C); CA with a thermal amplitude <30°C), will be included in the study and classified as "presumed CAD".

7.1 DESCRIPTION OF THE STUDY DESIGN

This is a European, multicenter, observational study of all adult patients with a CAD diagnosis from January 1st, 2009 through January 1st, 2019 seen at hematology/oncology centers in Germany, Italy and Austria.

This observational study plans to collect information on the thromboembolic risk and mortality in CAD patients. Data will be extracted retrospectively from the initial date of CAD diagnosis until the earliest of death, end of data availability (*i.e.* lost to follow-up) or end of data collection set on January 1st, 2020 for approximately 170 patients in total. The design of the study will mirror real life management of these patients.

Pseudo-anonymous subject-level data will be transcribed, retrospectively, from medical records onto electronic case report forms (eCRFs) by study investigators routinely involved in the management of these patients (or delegates at the study site). No examinations or procedures apart from those occurring as part of the patient's routine clinical care are required for this study.

Chart reviews will be performed regardless of whether patients are alive at the time of data collection. In order to include the maximum follow-up data available per patient, patient's medical records will be abstracted retrospectively from initial clinical manifestation of CAD until death, loss to follow-up or end of data collection, whichever comes first. There will be no prospective follow-up period.

7.2 DURATION OF STUDY PARTICIPATION FOR EACH PARTICIPANT

There will be no prospective follow-up period.

8 SELECTION OF PARTICIPANTS

8.1 NUMBER OF PARTICIPANTS

It is planned to globally recruit approximately 170 participants in up to 12 centers in the 3 countries of interest (Germany, Italy and Austria).

At each site, all CAD patients diagnosed between January 1st, 2009 and January 1st, 2019 will be screened to confirm their eligibility against all study inclusion and exclusion criteria (a screening form will be provided online to support patient screening).

8.2 INCLUSION CRITERIA

Patients must meet all the following criteria to be eligible for the study:

- Patient aged ≥18 years
- Patient who fully meet the diagnostic criteria per section 7.1:
- Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study. A request for a waiver of informed consent for patients deceased, lost to follow up or alive but did not visit the site at time of data collection will be requested, where applicable.

8.3 EXCLUSION CRITERIA

Patients who exhibit any of the following must be excluded from the study:

- Patient with any form of hemolytic anemia other than CAD, including CAS and mixed AIHA
- Presence of records of any cause of secondary CAS at diagnosis [concurrent diagnosis of any type of lymphoma, multiple myeloma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, other active cancer, or recent infection with mycoplasma pneumoniae Epstein-Barr virus, cytomegalovirus, autoimmune disorders (SLE)]

8.4 MODALITIES OF RECRUITMENT

Primary medical records will be available for review from specialty clinics treating CAD patients who agreed to participate in the patient chart review following a feasibility study.

Using the online screening form, study investigators routinely involved in the management of CAD patients (or delegates at the study site) will screen medical records of their patients diagnosed with CAD between January 1st, 2009 and January 1st, 2019 in a consecutive, retrospective order and include all those who fulfil pre-defined study eligibility criteria. Patient selection will be based on systematic sampling, *i.e.* all consecutive eligible patients are expected to be included in the study. Target sample size will be approximately 170 charts.

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9 SELECTION OF INVESTIGATORS

A list of sites managing CAD patients in each participating country will be designed by Cerner Enviza and the Sponsor based on data availability and characteristics of the health care system of each study country. In Germany, a comprehensive list of hematology and oncology hospitals potentially managing CAD patients across the country will be created from several sources, including Orphanet and PubMed. In Italy and Austria, a list of referral centers managing CAD patients based on existing input from pre-marketing clinical studies, local affiliates of the Sponsor and external advisors will be used for site selection.

A feasibility study will be run to select study sites from such lists. A site qualification questionnaire tailored to the study and country will be designed to evaluate feasibility and verification of the capability and willingness of the potential sites to complete the study. During the feasibility stage, research assistants will contact physicians from each site for completion of the site qualification questionnaire over the phone or via email to determine both site and physician eligibility to participate in the study. If a physician does not qualify for the study or refuses to participate in the study, he/she may refer another physician in the same hospital. If he/she qualifies but refuses to participate, the reasons for non-participation will be reported.

Within each country, the target number of centers participating in the study will be determined based on the capacity of each participating center to access patients meeting the eligibility criteria, as assessed by the feasibility study. Target number of centers may be adjusted accordingly.

Investigator selection will be performed independently in each country based on the feasibility assessment and eligibility criteria listed below.
Investigators may be hematologists, onco-hematologists or any other specialists involved in the management of adult CAD patients. Their eligibility will be based on the following criteria:

- Physicians working in centers managing patients with CAD and having available the appropriate facilities or equipment to perform research.
- Personally managing CAD patients
- Assessing or managing the thromboembolic risk in their CAD patients, or being informed by colleagues when their CAD patients present with a thromboembolic risk
- Agreeing to comply with the study protocol and data collection procedures.

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10 DATA COLLECTION

10.1 DATA COLLECTION SCHEDULE

Pseudo-anonymized epidemiologic, clinical, and biologic data from patient's medical charts will be extracted by site staff from the initial date of CAD diagnosis until the earliest of death, end of data availability (*i.e.* lost to follow-up) or end of data collection set on January 1st, 2020. Diagnosis must have occurred between January 1st, 2009 and January 1st, 2019. Duration of follow-up will depend on time of diagnosis; a priori, enrolled patients diagnosed earlier during this time period will have a longer follow-up period than those diagnosed later. There will be no minimum duration of follow-up. However, HCRU analysis will require having data from patient medical records available for a minimum of time following a TE to ensure all costs associated with each TE are covered. Per-patient-per-month (PPPM) HCRU will be calculated during the variable follow-up period of up to 12 months after the TE diagnosis.

There will be no prospective follow-up period. No examinations or procedures apart from those occurring as part of the patient's routine clinical care are required for this study.

The schedule of events is described in Table 2: Schedule of Recommended Study Assessments

Since this study is retrospective in nature, results will be collected as available.

Table 2: Schedule of Recommended Study Assessments

Data to be collected	Assessments	Screening	Baseline	Follow-up
Eligibility criteria		X		
Written informed consent (IC)		X		
Demographics			X	
Medical History	Comorbidities; TE risk factors		X	X
CAD diagnosis history and disease status	Clinical findings; indicators of anemia and hemolysis		X	X

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Significant medical events	TE dates and types; previous history of TE		X	X
Relevant treatment history	CAD-specific treatment patterns; response to treatment		X	X
Direct HCRU related to TE	Hospitalizations and length of stay; outpatient, ER and ICU visits			X
Patient vital status	Cause of death; date of death			X

10.2 DEFINITION OF SOURCE DATA

The primary data source for the study will be the patient medical record. All data will be captured in an electronic case report form (eCRF) and entered into an EDC system by the trained local site staff. No visits, examinations, or procedures apart from those occurring as part of the patient's routine clinical care are mandated as part of this study.

10.3 DATA COLLECTED

10.3.1 Participant data

Variables including but not limited to the following will be collected if available:

1. Demographics:
   1.1. Date of birth (month, year); Sex

2. Relevant medical history
   2.1. Any chronic or serious disease other than CAD and diagnostic date (e.g. AIHA; autoimmune disorders other than AIHA; known thrombophilia).
   2.2. Comorbidities: known thrombophilia; cardio-vascular conditions (CVCs): diabetes, hypertension, and hyperlipidemia; organ failure; cured or inactive malignant diseases; respiratory or cardiac deficiency; renal disease; hepatitis; inflammatory rheumatic disease ; obesity).

3. CAD characteristics
   3.1. Age at onset of anemia
   3.2. Age at CAD diagnosis
   3.3. Clinical presentation at or before diagnosis (*e.g.* circulatory symptoms: acrocyanosis; anemia; fatigue; jaundice; shortness of breath; asthenia; dyspnea; hemoglobinuria; angina)
   3.4. Biological features at diagnosis (e.g. haemolytic screen at diagnosis (hemoglobin level (g/L), Lactate dehydrogenase (LDH) level (UI/L), haptoglobin, bilirubin (µmol/L), reticulocyte (count); DAT pattern; cold agglutinin titer at 4oC; thermal amplitude)
   3.5. Disease status over follow-up (*e.g.* history of hemolytic exacerbation/flares; markers of disease activity/indicators of hemolysis: (*e.g.* hemoglobin level (g/L), lactate dehydrogenase (LDH) level (UI/L), haptoglobin, bilirubin (µmol/L), reticulocyte count)
   3.6. Transfusion history (*e.g.* number of RBC units transfused and dates)

4. Thromboembolic events
   4.1. Type of TE events (arterial, venous) and other events such as post-thrombotic syndrome and pulmonary hypertension, and dates
   4.2. Conditions in the weeks prior to a TE (*e.g.* chemotherapy, immobilization; thromboprophylaxis; TE-related hospitalization, major surgery; trauma; fracture; oestrogen and progestrogene use; pregnancy/puerperium)

5. CAD history treatment
   5.1. Drug therapy (*e.g.* agent/s, daily dose for corticosteroids, duration of therapy), line of treatment and treatment response (complete response, partial response, non-response)
      5.1.1. Any Corticosteroid Containing Therapy (betamethasone, budesonide, dexamethasone, steroid, prednisone, prednisolone, methylprednisolone); Any Rituximab Containing Therapy; Bortezomib; Bendamustine, Eculizumab;
   5.2. Splenectomy
   5.3. Thromboprophylaxis

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6. Direct HCRU associated with TE
   6.1. Inpatient admission dates and hospitalization length of stay (LOS)
   6.2. Outpatient visit dates
   6.3. ICU admission dates and LOS
   6.4. Emergency room (ER) visit dates
   6.5. Surgical and other major procedures related to CAD/TEs

7. Patient vital status
   7.1. Cause of death
   7.2. Date of death

A complete description of variables will be detailed in the Statistical Analysis Plan (SAP). All study data will be recorded according to the schedule of recommended assessments as outlined in Table 2. However, completion of a particular assessment will be at the discretion of the participating investigator and dependent on local standards of care and individual physician practice patterns. It is anticipated that death may not be always recorded in real-world practice, which may result in an under-estimation of mortality rates in the CAD population.

10.3.2 Site/Investigator questionnaire

Not applicable

10.3.3 Participant tracking log (if applicable)

In all countries, two different enrolled patient identification logs will be documented: one specific log for patients who signed an informed consent form, another specific one for dead patients, lost to follow up patients and for alive patients who did not visit the site during the data collection period. At the time of the database lock, and before the analysis, the specific enrolled patient identification log documented for dead patients, lost to follow up patients and for patients who did not visit the site during the data collection period and where the unique identifier is documented will be destroyed by the site. Therefore, collected data will not be identifiable for these patients.

10.4 PROCEDURE AND CONSEQUENCE FOR PARTICIPANT WITHDRAWAL FROM STUDY

Patients can withdraw from the study at any time, without giving a reason and without any penalty or loss of benefits to which they are otherwise entitled and without any effect on their future medical care. Should consent be withdrawn, data already collected up to the date of consent withdrawal will continue to be processed, but no new data will be collected.

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11 MANAGEMENT OF DATA

11.1 DATA COLLECTION, VALIDATION AND DATA QUALITY CONTROL AT CERNER ENVIZA LEVEL

Data will be entered at the site by the treating physician or an authorized staff member, into the electronic case report forms (eCRFs), which will be administered through the study Electronic Data Capture (EDC) system. Data will be entered into eCRFs in accordance with eCRF instructions. Each study investigator has ultimate responsibility for the collection and reporting of all data entered on the eCRFs and for ensuring that they are accurate, authentic / original, complete, consistent, and legible. Only authorized personnel will have access to the eCRF.

An eCRF should be completed for each subject. The completed eCRFs are the sole property of Sanofi-Aventis Groupe and should not be made available in any form to third parties, except for authorized representatives of Sanofi-Aventis Groupe or appropriate regulatory authorities, without written permission from Sanofi-Aventis Groupe. Any corrections to entries made in the eCRFs must be dated, initialed and explained (if necessary) and should not obscure the original entry. The eCRFs must be signed or approved by the study investigator or by an authorized staff member to attest that the data contained in the eCRFs is true.

All electronic data collection material hosted on the secure study web portal in European Union will include programming of electronic data checks, edit checks depending on data previously entered and automatic queries to make sure that the core variables are provided, and that the data entered is within a plausible range.

The computerized handling of the data by Cerner Enviza may generate additional requests to which the participating Investigator is obliged to respond by confirming or modifying the data questioned.

Data from the eCRFs will be compiled into a single, pseudo-anonymized dataset.
Data collection and validation procedures will be detailed in appropriate operational documents.

11.2 MONITORING AND DATA QUALITY CONTROL AT SITE LEVEL

During study conduct, Cerner Enviza (or their designee) will perform routine remote oversight of the sites' data collection activities and may also conduct periodic on-site monitoring visits ~~(except in Germany where no on-site visit will be conducted)~~ to ensure that the protocol is being followed. If applicable, during on-site visits, the monitors may review source documents to confirm that the data recorded is accurate. All information recorded in the study eCRFs must be consistent with the patients' source documentation (i.e., medical records).

Data entered into the database will be verified/validated as documented in components of the data management plan (DMP). Data cleaning specifications will include consistency and plausibility checks on data, as well as rules for data handling (e.g., process for query creation/closure, process for listing data review, process for missing and non-conformant data review, process for data handling and validation of electronic records; process for medical coding of data, process for collection of investigator signature, process for freeze/lock of the clinical database).

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12 PHARMACOVIGILANCE

The study is a non-interventional, descriptive, retrospective study based on secondary data collection from medical records of patients.

The design of such studies is characterized by secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses.

For these studies, the submission of suspected adverse reactions in the form of ICSRs (Individual Case Safety Reports) is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification (see GVP Module VIII).

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

Given the rarity of CAD, the number of patients included in the study is expected to be small. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable. Table 3 presents expected levels of precision (95% CIs) for estimating a proportion of the primary outcome (*i.e.* TE rates in CAD) for various scenarios with different incidence rates depending on the total patient counts expected to be recruited.

Table 3: Estimated 95% confidence intervals for a population proportion according to expected patient counts of CAD patients

	95% CI, TE proportion				
	proportion TE				
sample size (n)	0,30	0,25	0,20	0,15	0,10
180	0.23-0.37	0.16-0.29	0.14-0.27	0.10-0.21	0.036-0.15
170	0.23-0.37	0.17-0.31	0.14-0.27	0.10-0.21	0.06-0.16
160	0.23-0.38	0.18-0.32	0.14-0.27	0.10-0.21	0.06-0.16
140	0,23-0,38	0,18-0,33	0,14-0,28	0,09-0,22	0,06-0,16
120	0,22-0,39	0,17-0,34	0,13-0,28	0,09-0,23	0,05-0,17
100	0,21-0,40	0,17-0,35	0,13-0,29	0,09-0,23	0,05-0,18
80	0,20-0,41	0,16-0,36	0,12-0,30	0,08-0,25	0,04-0,19
60	0,19-0,43	0,15-0,38	0,11-0,32	0,07-0,27	0,04-0,20

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Assuming a TE incidence rate of 20-30% in CAD patients and a total sample of 170 CAD patients, the margin of error in the TE subgroup will be within ± 6.0 and 6.9% with an α risk of 95%.

13.2 DISPOSITION OF PARTICIPANTS

The following data will be presented to describe the patients' disposition:

- Number and percentage of patients belonging to the analysis population.

13.3 ANALYSIS POPULATIONS

Analysis population contains all patients who met the inclusion criteria and none of the exclusion criteria and were documented into the study.

13.4 STATISTICAL METHODS

This study is primarily descriptive in nature and does not include formal statistical hypothesis testing. A formal statistical analysis plan (SAP) that will provide details of all analyses and presentation of study data will be approved prior to database lock. All final analyses will be performed once the data from all patients has been collected in the database, cleaned and database lock has occurred.

All variables will be summarized descriptively through tabular displays of mean, median, ranges and standard deviations (SD) of continuous variables and frequency distributions of categorical variables. Changes in disease activity closest to the date of each study event will be described, where data are available. Crude incidence rates (with 95% CI) will be calculated from the number of TE after CAD diagnosis and the sum of individual person-years contributed by the CAD population during the study period. The mortality rate will also be estimated in this way. For event analysis, the main events evaluated will include time to first TE and time to death. The cumulative incidence of TE will be estimated using Kaplan-Meier survival analysis accounting for mortality as a competing risk event if sample size allows it.
Descriptive analysis will be used to identify risk factors associated with occurrence of TE.

Due to the potentially variable length of follow-up, HCRU will be calculated as per-patient-per-month (PPPM) during the variable follow-up period of up to 12 months after the TE diagnosis. Patients with both "confirmed" and "presumed" CAD will be included in the primary analysis. Sensitivity analysis will be performed to address any potential misclassification in CAD diagnosis; patients who fully meet the inclusion criteria will be classified as having "confirmed CAD"; reported patients who were diagnosed with CAD but whose medical records do not capture all the data required to define CAD or distinguish CAD vs CAS using strict haemato-immunologic diagnosis criteria will be classified as "presumed CAD".

Depending on scientific interest and the distribution of the data, exploratory analyses may be conducted to examine other research questions, *e.g.* TE-free survival curves may be derived for individuals with none versus one or more CAD-related TE risk factors.
A specific analysis will be conducted for Italy.

Patients' records will not be excluded because of missing data, and missing data will not be imputed. The base relevant to each analysis will be reported alongside the percent of missing data in tables provided for all descriptive analyses.

As the data are analysed, some deviation from planned analysis may be anticipated (*e.g.*, missing data, small sample size). Therefore, the SAP may modify the plans outlined in the protocol; any major modifications would be reflected in a protocol amendment.

All statistical analyses will be carried out using standard statistical software, including SAS, Stata, R as appropriate.

13.5 EARLY ANALYSIS

An interim analysis will be performed when the documentation of two out of three countries is completed, and when minimum number of patients have been included in two countries. It will be described in the Statistical Analysis Plan.~~No interim analysis is planned to be conducted.~~

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14 RESPONSIBILITIES

14.1 RESPONSIBILITIES OF STUDY COMMITTEES

No study committees are anticipated.

14.2 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigator will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator's responsibility to:

- Obtain written informed consent from participants prior to inclusion in the study,
- Fill in the CRF and to record all data pertinent to the study. She/he will ensure that the information reported in the CRF is precise and accurate.

The Investigator or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the participant of all pertinent aspects of the study including the written information. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a participation in the study, the written informed consent form (ICF) should be signed, name filled in and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the participant.

14.3 RESPONSIBILITIES OF CERNER ENVIZA

Cerner Enviza is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

Cerner Enviza will be responsible for all activities from the design of the study methods to analysis of the data and delivery of the results. Cerner Enviza, via local affiliates or partners, will notably be in charge of local submission(s) to ethical committee(s) complying with data protection rules and any other local submission(s).

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15 ETHICAL AND REGULATORY STANDARDS

15.1 ETHICAL PRINCIPLES

This study will be conducted in accordance with the principles laid by the 18 World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

15.2 LAWS AND REGULATIONS

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiology Practices (GPP). Each participating country should locally ensure all necessary regulatory submissions (e.g, IRB/IEC submission if applicable) are performed in accordance with local regulations including local data protection regulations.

16 ADMINISTRATIVE EXPECTATIONS

16.1 RECORD RETENTION IN STUDY SITE

The Investigator shall arrange for the retention of study documentation until the end of the study.

In addition, the Investigator will comply with specific local regulations/recommendations with regards to participant record retention.

It is recommended that the Investigator retains the study documents for at least 5 years after the final report or discontinuation of the study, unless otherwise specified in the Investigator Agreement, in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

16.2 CONFIDENTIALITY

All material, information (oral or written) and unpublished documentation provided to the Investigator (or any action carried out by Cerner Enviza on their behalf), including the present protocol and the CRF, are exclusive property of Cerner Enviza.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of Cerner Enviza.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

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16.3 DATA PROTECTION

All personal data collected related to study participants, Investigators, or any person involved in the study, shall be treated in compliance with all applicable national and international data protection and privacy laws and regulations, including the Regulation (EU) 2016/679 (General Data Protection Regulation – GDPR). The study Sponsor is the Sanofi-Aventis Groupe responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi-Aventis Groupe databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objectives.

Participants will be assigned a unique identifier that will be automatically allocated by the study application at completion of the patient screening. For data quality control procedures (including queries) and audit purpose only, the investigator will keep a record of the number allocated to each eligible patient together with their nominative data in two different enrolled patient identification logs: one specific log for patients who signed an informed consent form, another specific one for dead patients, lost to follow up patients and for alive patients who did not visit the site during the data collection period. At the time of the database lock, and before the analysis, the specific enrolled patient identification log documented for dead patients, lost to follow up patients and for patients who did not visit the site during the data collection period and where the unique identifier is documented, will be destroyed by the site at the time of database lock, and before the analysis. Therefore, collected data will not be identifiable for these patients. Any datasets that are transferred to the Sponsor or its service providers will be pseudo-anonymized; no identifiable data will be transferred to the Sponsor, nor Cerner Enviza.

The participant must be informed that her/his personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the participant and summarized in the informed consent.

The participant must be informed that her/his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Participants must be informed that their study-related data will be used for the whole "drug development program", i.e, for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (e.g, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi-Aventis Groupe to manage involvement in the study and/or the related contractual or pre contractual relationship. They may be communicated to any company of the Sanofi-Aventis Groupe or to Sanofi-Aventis Groupe service providers, where needed.

- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi-Aventis Groupe Data Protection Officer (link available at Sanofi.com).

- In case of refusal to the processing of personal data by or on behalf of Sanofi-Aventis Groupe, it will be impossible to involve the professionals in any Sanofi-Aventis Groupe study. In case the professionals have already been involved in a Sanofi-Aventis Groupe study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.

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primary data collection

Study Number: GER-CAD-19-11180 Version number: ~~V6~~V7.0

- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi-Aventis Groupe or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi-Aventis Groupe in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi-Aventis Groupe's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi-Aventis Groupe leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi-Aventis Groupe for up to thirty (30) years, unless further retention is required by applicable regulations.

- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi-Aventis Groupe participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi-Aventis Groupe with other pharmaceutical company

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members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.

- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi-Aventis Groupe Data Protection Officer (DPO): Sanofi DPO - 46 avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi-Aventis Groupe by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy policy/contact).

16.4 DISSEMINATION OF STUDY DATA

Study participants

Sanofi-Aventis Groupe shares information about clinical studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, as well as some national registries.

Results from clinical studies in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. In addition, results may be provided on Sanofi.com in the form of link to the journal or summary result. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical studies. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study

Sanofi-Aventis Group may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

16.5 INSURANCE

No insurance is required since it is an observational study with no risk to the participants. The study will operate under real clinical practice conditions. However, participating countries may contract insurance according to local specific requirements.

16.6 SANOFI-AVENTIS GROUPE OR CERNER ENVIZA AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

The Investigator agrees to allow Sanofi-Aventis Groupe and Cerner Enviza auditors/Competent Authorities inspectors to have direct access to her/his study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, she/he will inform Cerner Enviza and authorize Cerner Enviza to participate in this inspection.

The confidentiality of the data verified and the protection of the participants should be respected during these inspections.

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Any result and information arising from the inspections by the Competent Authorities will be immediately communicated by the Investigator to Cerner Enviza.

The Investigator shall take appropriate measures required by Sanofi-Aventis Groupe or Cerner Enviza to take corrective actions for all problems found during the audit or inspections.

16.7 PREMATURE DISCONTINUATION OF THE STUDY

Sanofi-Aventis Groupe can decide at any time and for any reason to prematurely stop or to interrupt the study; the decision will be communicated in writing to the Investigator.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to immediately inform Cerner Enviza in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

16.8 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of Sanofi-Aventis Groupe.

16.9 PUBLICATIONS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Scientific Committee/coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

17 PROTOCOL AMENDMENTS

Any change to the protocol will be recorded in an amended version of the protocol, which will be signed by the Investigator and may require regulatory submissions (eg, IRB/IEC) in accordance with local regulations.

In some cases, an amendment may require a change to the ICF.

Name	Date	Version	Description of changes:
Jérôme Dubard Cerner Enviza Project Manager	27-Jul-2023	V7.0	○ Change of Sponsor's signatory, ○ Study timelines have been updated, ○ On-site monitoring activities have been updated, ○ Interim analysis has been added and specific report for Italy deleted.
Jérôme Dubard Cerner Enviza Project Manager	31-Jan-2023	V6.0	○ New Sponsor address, ○ New Sponsor DPO address, ○ Study timelines have been updated, ○ Request of waiver added for lost to follow up patients and alive patients who did not visit the site during the data collection period in Inclusion criteria (synopsis and section 8.2), ○ Section 10.3.3 has been developed and is now applicable. Related text in section 7.1 has been

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			deleted and moved to this section, o Precision added in section 16.1 “Record retention in study site” o Precisions added in sub-section “Protection of participant data” in section 16.3.
Jérôme Dubard Cerner Enviza Project Manager	05-Oct-2022	V5.0	o Following German Ethics Committees requests, clarifications about data protection have been added in the synopsis and sections 7.1 and 11.1, 11.2 and 16.3, o CRO address and name have been updated from Kantar Health to Cerner Enviza, o Sponsor address and name have been updated from Sanofi US to Sanofi-Aventis Groupe, o Sponsor name has been harmonized with Sanofi-Aventis Groupe throughout the protocol, o Study timelines have been updated, o Country specific report added for Italy.

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Specificities

Clinical Sciences & Operations		
G - Manage Medical & Quality Requirements	G.6 - Medical and Clinical Quality	
Q - Product Life-cycle Processes	Clinical Development, Post-Authorization Studies and Programs	No Subsystem

Applicability

Entity / GBU	Clinical Operations (CRO)	Customer Health Care	Diabetes and Cardiovascular
	General medicine and Emerging Market	Specialty Care	
Geography	Europe		
Applications Services	Clinical Sciences & Operations	Global Pharmacovigilance	Global Regulatory Affairs
	Medical, Clinical & Country Quality		

Related documents

Reference	Title
QSOP-002178	Preparation and Approval of Study Outline, Extended Synopsis, Abbreviated Protocol, Protocol, and Amended Protocol